5-2021

Neurological and Psychological Effects of COVID-19 on Cognitive Impairment

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A Capstone in Neurobehavioral Sciences by Saba Mufti

Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Biomedical Sciences, Neurobehavioral Sciences Concentration

May 2021

ABSTRACT

Increasing evidence suggests that individuals affected with COVID-19 may be at high risk for developing long-term neurological consequences (Heneka et al., 2020). Psychological stress may also increase risk in cognitive impairment, which can lead to mental fatigue. However, research studies suggest that there is a relationship between physiological and psychological factors affecting cognitive function (Scott et al., 2015). The mechanistic understanding of neurological symptoms in patients affected with COVID-19 regarding whether they emerge from mental illness or directly from the invasion of SARS-CoV-2 into the central nervous system is limited (Mahammedi et al., 2020). Factors affecting the brain can lead to mental fatigue, which is a type of condition that is triggered when the use of cognitive activity is extended for a long period of time (Penner & Paul, 2017). Although certain neurobehavioral abnormalities can arise from COVID-19, measuring the abnormalities objectively poses an issue due to lack of objective testing. Cognitive impairment can have a considerable negative impact on everyday social activities and quality of life, making this a challenging topic for both healthcare professionals and patients (Jonasson et al., 2018). Identifying risk factors that can be modified prior to developing cognitive impairment, especially during an individual's midlife, also represents a challenge in improving one's overall quality of life as well as controlling the costs of healthcare (Scott et al., 2015). Therefore, understanding neural mechanisms underlying cognitive processing may contribute towards developing future treatment strategies that will help individuals suffering from cognitive impairment. Several studies have shown which regions of the brain are affected by an infection with

the SARS-CoV-2 virus (Radmanesh et al., 2020; Katal & Gholamrezanezhad, 2021). Additional studies analyzed the effect of COVID-19 and stress on cognitive function through methods involving questionnaires to obtain information to determine participants' psychological morbidities and fatigue, a neuropsychological assessment of COVID-19 patients to measure different aspects of neurocognitive functioning, and surveys such as KAP (Knowledge, Attitudes, and Practices) model (Qi et al., 2020; Almeria et al., 2020; Morgul et al., 2020). Researchers have found that there are methods which can be used to assess and measure certain factors that affect cognitive functioning. The findings of these studies will improve one's understanding of environmental, physiological, and psychological factors that can lead to cognitive impairment. This will also allow researchers to measure certain factors as well as to discover ways to intervene and prevent potential targets that may cause cognitive impairment due to COVID-19. Therefore, psychological stress should be considered in this regard since this risk factor essentially represents a target for prevention and intervention strategies (Scott et al., 2015).

BACKGROUND

Psychological stress is one of the risk factors that can lead to development of cognitive impairment in both the short-term and long-term (Scott et al., 2015). COVID-19 has been shown to potentially cause cognitive dysfunction in patients affected by this virus both psychologically and neurologically. COVID-19 was declared as a global public health emergency because viral surges have been affecting people worldwide (Zhou et al., 2020). This pandemic affects both individuals with pre-existing mental illnesses as well as healthy individuals that have anxiety and feelings of worry (Nami et al., 2020). COVID-19 caused people to deviate from their normal life routine because of the challenge of performing everyday activities that emerged from the pandemic. The invoked feelings of fear and anxiety in individuals are due to factors such as isolation, quarantine and contagion. This may lead to chronic stress and hence could have an association with a burden on mental health. The COVID-19 pandemic created a challenge to psychological resilience.

According to Burtscher et al. (2020), chronic stress tends to be a strong modulator of immunity, which in turn influences a chance that infection will occur. Chronic stress also elicits structural and functional consequences of the brain. Because of this, social behaviors become altered and result in individuals being limited in their ability to cope with stress that arises from the pandemic. In other words, stress-related consequences of COVID-19 leading to individuals attaining chronic stress and triggering their impairment in coping with stressful situations may also lead to immune system capacity issues as well as alterations in structure and function of the brain (Burtscher et al., 2020).

Although clinical and epidemiological features of COVID-19 manifested in affected patients have been pointed out, the psychological impact of this virus such as cognitive function remains unclear (Qi et al., 2020; Zhou et al., 2020). COVID-19 was predominantly thought of as a respiratory virus when initially discovered. Patients affected with COVID-19 would complain about being unable to breathe. However, current research has revealed how the severe form of the virus tends to be associated with neurological deficits. Individuals diagnosed with COVID-19 may have a higher risk for developing neurological consequences even after recovering from the infection (Beaud et al., 2020; Heneka et al., 2020). Reports mentioned that COVID-19 patients experienced neurological symptoms including headaches, cerebrovascular disease, and neuralgia. Other symptoms may develop in COVID-19 patients as well, including shortness of breath, new loss of smell, and congestion (Kempuraj et al., 2020). COVID-19 primarily acts on respiratory targets, but neurological damage also has the potential to occur. One study discusses how the coronavirus could potentially be neurotropic, which is a virus that is capable of invading and affecting the neural tissue (Katal & Gholamrezanezhad 2021). Steardo et al. (2020) mentioned that viral neurotropism, systemic infection, and environmental stress together may aggravate the COVID-19 pandemic situation as they may contribute to developing psychiatric pathologies. Therefore, the COVID-19 neuropsychiatric sequelae presents a clinical challenge for individuals suffering from the pandemic (Steardo et al., 2020).

REVIEW OF STUDIES

Factors causing brain damage can result in individuals suffering from mental fatigue, which is a type of condition that occurs when triggered by an extended duration of cognitive activity and can be long-lasting. After someone experiences a brain injury, that individual may undergo extra effort in their thinking process; this extra work that the brain performs can result in fatigue. Jonasson et al. (2018) referred to this phenomenon as the coping hypothesis, which suggests that the brain needs to perform certain tasks harder to compensate for impaired cognitive functions. The brain working harder than normal can result in mental fatigue, which in turn, can lead to cognitive impairment. This may negatively impact an individual's quality of life and his or her participation in everyday social activities. Mental fatigue, therefore, is a challenging topic to deal with for both healthcare professionals as well as for patients that experience cognitive impairment (Jonasson et al., 2018). Hence, understanding neural mechanisms underlying cognitive processing becomes important as this can contribute to developing future treatment strategies that will help individuals suffering from cognitive impairment due to COVID-19. While no effective treatment has been found yet to reduce the negative impact COVID-19 has on psychological health, other treatment methods that can be taken into consideration include symptomatic treatment and supportive care (Renjun et al., 2020).

Despite evidence that stress may increase susceptibility to cognitive impairment, there is minimal evidence regarding the psychological and physiological mediators of the relationship between cognitive function and stress (Scott et al., 2015). Research supports patterns of certain stressors regarding the effect of cognitive function by psychological

stress in the short-term and long-term. For instance, individuals appraising stressful events may overuse their cognitive resources and cope with demands that can lower cognitive performance. Stress occurring on a daily basis has also been shown to increase inflammation and negative mood in the short-term, which are typically associated with fatigue (Scott et al., 2015).

Aside from the neurological aspect of COVID-19's effect on individuals, research has also shown how the COVID-19 pandemic tends to instill stress and increase the chances of causing mental health issues. Fofana et al. (2020) discusses how emergencies imposed by healthcare regulators led to adverse effects on mental health, therefore increasing cases of depression, anxiety, and other associated mental illnesses. Even the thought of COVID-19 is creating negative emotions such as fear and tiredness, which may establish a burden in individuals' internal capacities and cause issues in skills such as decision-making and thinking (Fofana et al., 2020).

A long-term impact that is increasingly apparent with regards to COVID-19 is the virus's effect on cognitive function. According to Baker et al. (2020), about 1 in 3 patients who recover from COVID-19 may experience psychological or neurological symptoms afterwards. This may reflect a growing issue that COVID-19 can create a lasting impact on the brain (Baker et al., 2020). As the number of COVID-19 cases increases, so have neurological symptoms and psychological illnesses. Not only has mental health issues such as depression and anxiety become greatly affected because of social distress, the coronavirus also is known to affect the central nervous system in the brain, leading to neurological issues (Nami et al., 2020). Common neurological manifestations include headaches, myalgias and loss of smell. One study considers these

symptoms as direct effects of COVID-19 on the central nervous system (Amelia et al., 2020).

Psychological stress is a major factor incurring from COVID-19, which solidifies the importance of helping individuals deal with their stressful reactions. While some evidence exists that links stress and cognitive function, only a few studies have assessed certain mediators as a way to analyze how stressful experiences affect cognitive functioning. Theorists specializing in stress have hypothesized a pathway known as unconstructive repetitive thinking (URT). This is involved in an important role of conveying the effects of stress on both somatic and mental health because of the idea that stressful experiences tend to negatively affect cognitive health (Scott et al., 2015).

Some studies evaluated the effects of stress on cognitive loss and how mental fatigue leads to impaired cognitive function, while other studies performed neuroimaging techniques for analyzing mental fatigue. Kempuraj et al. (2020) discussed how COVID-19 causes psychological stress for individuals, which can lead to or exacerbate mental illnesses. They suggest that COVID-19 may cause many neurological issues including headache, stress, stroke and cerebrovascular dysfunction. The authors of this publication also discussed how COVID-19 can induce psychological stress, leading to neuroinflammation (Kempuraj et al., 2020).

COVID-19 also causes disruption in the blood-brain barrier (BBB), suggesting that the cytokine storm can cause more inflammatory mediators in the brain to enter the breached BBB. The BBB disruption may also allow SARS-CoV-2 to infiltrate in the brain (Kempuraj et al., 2020). Ebru Morgul et al. (2020) investigated how COVID-19 is

associated with psychological fatigue as a mental health concern by developing a COVID-19 knowledge questionnaire, which assesses various details including the participants' understanding of the coronavirus and their attitudes toward the coronavirus (Morgul et al., 2020). Nami et al. (2020) highlighted the associations between COVID-19 and the nervous system, as well as mental health illnesses. They also aimed to explore possible mechanisms of neural injury through psycho-neuroimmunity, which studies the interaction between psychological processes and both nervous and immune systems (Nami et al., 2020).

Questionnaires

Morgul et al. (2020)'s study was conducted in Istanbul, Turkey, where the authors focused on fatigue as one of the psychological outcomes of experiencing fear and anxiety of the COVID-19 pandemic. They assigned participants into two groups: the psychologically fatigue group and the normal group. The participants had to complete the Knowledge Attitude Practices (KAP) and the Fatigue Assessment Scale (FAS) questionnaires. The authors developed their own questionnaire that was divided into 5 sections. These sections include socio-demographic details, participants' knowledge on COVID-19, attitudes towards COVID-19, precautionary measures or practices that participants have taken, and the FAS questionnaire itself. FAS assesses both physical fatigue and mental fatigue through 10 questions that are self-reported (Morgul et al. (2020).

Mental Fatigue Scale

Since stress regarding COVID-19 can cause many psychological and neurological symptoms, assessing cognitive activity may help researchers understand what processes are affected in the brain. When individuals suffer from injury to the brain, mental fatigue is usually a common symptom that follows after (Jonasson et al., 2018). Mental fatigue is triggered when the duration of cognitive activity is extended (Penner & Paul, 2017). In a research article by Jonasson et al. (2018), the authors questioned whether or not mental fatigue can be measured objectively because an objective test for mental fatigue does not currently exist. They hypothesized that individuals who experienced brain injury and suffered from long-term mental fatigue will not show improvement on certain cognitive tasks, whereas the control group is able to improve (Jonasson et al, 2018).

In their study, the researchers recruited participants that met specific criteria and then assessed the participants' mental fatigue through an assessment questionnaire referred to as the mental fatigue scale (MFS). While this study assesses cognitive decline generally in individuals that experience a brain injury and was not used specially for COVID-19 patients, questionnaires can be taken into consideration in order to obtain more information of how COVID-19 symptoms can be managed.

Neuropsychological Assessment of Cognitive Impairment Related to COVID-19

Little is known regarding the association between COVID-19 and cognitive impairment. However, COVID-19 does have known neurotropism. According to Almeria et al. (2020), the neurological symptoms presented in COVID-19 patients were determinants for cognitive deficit. Some cognitive complaints in these patients include

symptoms of anxiety and depression. The authors performed a neuropsychological assessment on patients with confirmed cases of COVID-19. They excluded subjects with previous known cognitive impairment and any other psychiatric or central nervous system diseases. The researchers assessed cognitive impairment through a selection of subtests which were put together to create a neuropsychological battery for the selected participants. The types of cognitive functioning that were measured include learning and verbal memory. Their findings may be important with regards to detecting anxiety and depression early as this can help limit the number of cognitive complaints that COVID-19 patients may have (Almeria et al., 2020).

Neuroimaging Techniques

Radmanesh et al. (2020) performed neuroimaging techniques via MRI examinations on patients with confirmed diagnosis of COVID-19 and discussed possible pathogenesis that could be causes of these neuroimaging features. The researchers of this study performed brain imaging techniques in 11 patients with COVID-19 with persistent depressed mental status. The MRI was done according to a routine brain protocol. Patients from the study with leukoencephalopathy had symmetric T2 hyperintensities and mild restricted diffusion that involved deep and subcortical white matter. Diffuse leukoencephalopathy and certain microhemorrhages were the two types of brain features that were found and reported during brain imaging in individuals who were critically ill with COVID-19. One image that Radmanesh et al. (2020) provided in their publication showed multiple MRI scans of the brain at the level of the centrum semiovale in two COVID-19 patients that have diminished mental status. Some of the MRI brain scans

were of those from a 56-year old man while the other brain scans are from a 64-year old man. The scans demonstrated symmetric diffuse T2 hyperintensity, mild restricted diffusion, and deep and subcortical white matter (Radmanesh et al., 2020).

In addition to Radmanesh et al.'s (2020) publication, other studies including Katal & Gholamrezanezhad (2021) also summarized some of the common neuroimaging findings found in patients with COVID-19. With regards to those with abnormal neuroimaging findings, the common abnormalities that Katal & Gholamrezanezhad (2021) found included cortical signal abnormalities, hemorrhages, and meningitis/encephalitis among others (Katal & Gholamrezanezhad (2021). The data from these various publications are summarized and compiled in Table 1.

Comparing Neuroimaging Findings of Various Abnormalities in Patients Affected with COVID-19	
Publication	Findings
Radmanesh et al. (2020)	Symmetric diffuse T2 hyperintensity, mild restricted diffusion, deep and subcortical white matter
Katal & Gholamrezanezhad (2021)	Cortical signal abnormalities, hemorrhages, meningitis, encephalitis
Moonis et al. (2020)	Most common → Acute infarcts with large clot burden and intracranial hemorrhage Other imaging patterns → leukoencephalopathy, meningitis, encephalitis, involvement of the olfactory bulb
Lin et al. (2020)	Acute/subacute findings, cerebral infarctions, parenchymal hematomas, posterior reversible encephalopathy syndrome, cranial nerve abnormalities

Table 1. Comparison of Various Neuroimaging Abnormalities in Patients with COVID-19. This table summarizes and compares the different findings that were observed in multiple publications where researchers performed neuroimaging techniques on patients affected by COVID-19.

Therapeutic Interventions

A particular type of psychotherapy that can be considered for people who develop feelings of fear and anxiety regarding COVID-19 is cognitive behavioral therapy (CBT). CBT is a form of treatment that aims to reduce unwanted psychological symptoms. This can be especially suitable to help individuals regain control of their lives and reduce their negative feelings towards the pandemic. However, not having enough mental health care providers is a growing issue for those requiring psychotherapy. Alavi et al. (2020) discussed a virtual and digital method of psychotherapy as a solution to improve time efficiency of mental health care workers instead. The researchers focused on evaluating the effectiveness and viability of utilizing an online tool to help treat mental health problems provoked by stressors linked to the COVID-19 pandemic (Alavi et al., 2020).

Using online and digital methods can be considered for the treatment of mental health illnesses associated with the COVID-19 pandemic if in-person techniques are not feasible because some people may not want to get treated in person and would prefer an online alternative. This may also help mental health care providers as well because the demand for them is increasing, which is a challenge because increasing the number of mental health care providers is not easily or readily achievable. Different studies and the interventions they suggest for managing stress related to COVID-19 is shown in Table 2.

Suggested Therapeutic Interventions for Stress Management			
Intervention	Description	Purpose	Reference
Psychotherapy	Type of talk therapy that uses psychological methods	Educates and treats patients; eliminates physical symptoms and improve mental health	Renjun et al. (2020)
Online Psychotherapy / Digital Models	A variety of online, digital tools to help treat mental health issues	Similar to in-person psychotherapy in educating and treating patients, except delivered virtually and digitally	Alavi et al. (2020)
Clinical Interview	Clinical assessment that will collect information on a person's thoughts, emotions, and psychological issues	Promotes and enhances a person's well-being by determining whether that person requires a structured psychological treatment	Ferrario et al. (2021)
Positive Psychology Interventions (PPIs)	A psychological intervention that helps raise positive feelings, cognition and behavior	Supports adaptive coping with certain life stressors	Waters et al. (2021)

Table 2. Suggested Therapeutic Interventions for Stress Management
This table provides a summary of various psychological interventions that were discussed in various publications along with their description and goals to help individuals cope with COVID-19.

ESCAPE Project

The ESCAPE (Effects of Stress on Cognitive Aging, Physiology, and Emotion) project is used for examining how environmental, physiological, and psychological stress-related factors build up to affect cognitive health negatively. One primary goal of ESCAPE in this study in particular is to examine whether taking part in unconstructive repetitive thought (URT) serves as a significant psychological pathway where stressors may lead to adverse effects on cognitive health. Another major goal is to examine if

stress-related changes in the HPA-axis account for these relations between URT and cognitive performance decline at a physiological level. Therefore, the ESCAPE project may help prevent cognitive impairment and in turn promote cognitive health in the future (Scott et al., 2015).

This study aims to enhance understanding the biological and psychological mechanisms that help explain how life experiences can influence one's overall cognitive health and wellbeing. According to Scott et al. (2015), the protocol for the ESCAPE project includes four waves of data collection across a period of three years. During each wave, participants are expected to complete surveys, cognitive assessments and lab visits, as well as to provide saliva and fasting blood samples (Scott et al., 2015). Research regarding the connection between stressful experiences and cognitive function is limited even though there is evidence that psychological stress has some impact on cognitive decline (Scott et al., 2015). The ESCAPE project in Scott et al.'s (2015) study is used for the general assessment of stress. This project evaluates how stressful events affect cognitive health negatively and assesses stress, psychological mediators, biological mechanisms that occur within the body, and cognitive outcomes.

Although the ESCAPE project has not been used specifically for COVID-19 yet, this can be useful to assess stress-related events that impact individuals with COVID-19. Scott et al. (2015) discusses how instances such as experiencing stress and occupying one's thoughts with stressful encounters can lead to increased cognitive degeneration as well as diminished cognitive tasks. The COVID-19 pandemic is concerning for individuals as this instilled a great deal of tension and fear regarding how to deal with the various stressors. Having a method such as the ESCAPE project can help reduce that

stress and in turn, promote overall quality of life for those who suffer from anxiety related to the pandemic.

RESEARCH STRATEGIES

PubMed

Literature search was conducted through using specific keywords via the PubMed database and performing a systematic search on the topic of interest that was chosen. This was done to locate original journal articles that are relevant for discussing the neurological and psychological symptoms of COVID-19, their interrelations, and their impact on cognitive function.

DISCUSSION

COVID-19 is a widespread pandemic that is affecting people worldwide. This is causing stress in individuals who excessively worry about what may happen, leading to a symptom of fatigue. This stress can cause alterations in the brain; therefore, COVID-19 has the capability of producing neurological and psychological effects on the brain. Relevant studies were used to evaluate the neurological and psychological effects of COVID-19 on cognitive impairment and to assess various psychological interventions to help individuals overcome any stress they have towards the pandemic. With regards to the number of studies in which researchers performed neuroimaging in patients with COVID-19, multiple brain abnormalities in these patients have been found, including acute infarcts, meningitis, encephalitis and cranial nerve abnormalities. Neuroimaging can be helpful in understanding how the brain develops and changes in response to COVID-19, especially when there are neuroimaging patterns as they could help indicate any alterations or abnormalities in the brain.

Discussion regarding treatment options explained that in the prevalence of COVID-19, no effective medications have been found. However, suggestions have been made to focus more attention on psychological interventions which could improve COVID-19 symptoms. If some of the symptoms that individuals experience can be alleviated or reduced in some way, this can become beneficial for COVID-19 patients. Psychotherapy, as mentioned by Renjun et al. (2020), utilizes psychological methods that assist in educating and treating patients. This in turn can improve mental health and eliminate some of the symptoms. Because of the fear and anxiety that people develop due

to the COVID-19 pandemic, being able to reduce psychological stress via psychological intervention might be one of the solutions to relieve anxiety and prevent decline of immunity (Renjun et al., 2020).

Questionnaires and validated scales also helped acquire valuable information about people's attitudes and the psychological aspects of COVID-19. These empirical tools are essential for managing mental health issues, which can assist mental health professionals and researchers deal with the psychological aspect associated with the pandemic and in turn support those that are mentally affected by COVID-19. Using structured scales can also allow for understanding the effectiveness of interventions. Psychological resilience is a problematic challenge that arises from this pandemic since people are susceptible to fear and anxiety. This can lead to people developing psychiatric illnesses or psychological problems, even altering the structure of the brain.

RECOMMENDATIONS FOR FUTURE STUDIES

For future studies, performing methods that can help assess certain factors such as stress and their impact on the neurological and psychological consequences of COVID-19 may assist researchers in intervening and preventing potential targets that may lead to cognitive impairment due to COVID-19. Interventions such as stress management programs may help stress-related COVID-19 issues as well since those who experience high levels of stress may be detrimental to their overall mental health. Questionnaires can also be utilized to investigate the connection between the COVID-19 pandemic and psychological fatigue. While the Morgul et al. (2020) study was conducted in Istanbul, Turkey, this can be taken into consideration in other countries to help further address associations between COVID-19 and people's mental health. Since the issue that people have in response to the pandemic is the fatigue they acquire due to experiencing stress with regards to COVID-19, and that this leads to negatively affecting a person's psychological well-being, providing questionnaires may allow researchers to find coping strategies to deal with mental stress and fatigue. This can enhance the well-being of those that are affected by the pandemic and possibly reduce fatigue as a psychological consequence due to pandemic-related anxiety and fear (Morgul et al., 2020.)

Neuroimaging

Even though the studies that were mentioned described abnormalities of the brain in response to neurological symptoms of COVID-19, neuroimaging could also be helpful

in analyzing portions of the brain responsible for the elicited fear response, such as the amygdala.

Stress Management Interventions/Strategies

Since COVID-19 causes mental stress and panic, providing psychological interventions can help reduce the psychological burden on patients. Some COVID-19 patients tend to feel anxious; therefore, reducing psychological stress can help eliminate some of that burden and help individuals restore their everyday functioning in society (Renjun et al., 2020). Various interventions and strategies to combat fear and anxiety associated with the COVID-19 pandemic include psychotherapy, clinical interview/assessment, and positive psychology interventions (PPIs). Each of these strategies are summarized in Table 2.

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